

U.S. Application Serial No. 09/848,866  
Amendment dated January 26, 2005  
in response to Office Action mailed October 26, 2004

Docket No. SYRTECH 5001-U

**REMARKS/ARGUMENTS**

**Rejection Under 35 USC 112, Second Paragraph**

The Examiner rejects claims 1-7, 16, 21-25, 31-36, 38, 40, 42, 45, 48 and 52-57 under 35 USC 112, Second Paragraph on the grounds that the claims are indefinite.

The Examiner rejects independent claim 1 and the claims depending thereon on the grounds that it is not clear whether "different biomolecule structures" are different structures of the target molecule, or of different molecules, and, in the latter cases, are these different biomolecules, or 'different structures' of a different biomolecule." Applicants amend independent claims 1 and 52-57 to specify that the "group of different biomolecule structures" is a "group of structures of different biomolecules."

The Examiner rejects independent claim 1 and the claims depending thereon on the grounds that it is not clear "how the method arrives at identifying compounds with 'superior structural identity' because 'structural identity' is usually determined by comparison of structures, not by rotational and translational replacements performed in the course of multiple replacement search." Applicants amend claim 1 to specify that the comparison produces data that "predicts which biomolecule structures in the group have superior structural identity with the target biomolecule." Applicants note that a benefit of the present invention is its ability to predict which biomolecule structures would be expected to have superior structural identity with the target molecule and thus would be expected to be a superior search model to use in molecular replacement.

The Examiner rejects dependent claim 16 on the grounds that the degree of dissimilarity is unclear. In this regard, it is intended that the degree of dissimilarity be at least sufficient that both structures would not be expected to function as an effective search model for the same target molecule. Applicants amend claim 16 to reflect this intention.

Applicants submit that the claims, as amended are definite and respectfully request the Examiner to withdraw the pending rejection under 35 USC 112, Second Paragraph.

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**Rejection Under 35 USC 103(a)**

The Examiner rejects claims 1-7, 16, 21-25, 31-36, 38, 40, 42, 45, 48 and 52-57 under 35 USC 103(a) on the grounds that the claims are rendered obvious over the background information (pages 3-5) and Podjamy, et al. or Vitali, et al.

In support of the Examiner's rejection, the Examiner acknowledges that the references cited in the background section of the present application "describe molecular-replacement methods which use an existing 'search model' to analyze crystal data of the target molecule." The Examiner then relies on Podjamy, et al. and Vitali, et al. for teaching the use of multiple search models.

Applicants amend independent claims 1 and 52-57 to specify that the "group of different biomolecule structures" is a "group of structures of different biomolecules" which distinguishes both Podjamy, et al. and Vitali, et al. As discussed below, unlike these two cited references, the pending claims teach methodology for selecting which biomolecule from a plurality of biomolecules has a structure that is anticipated, based on the method, to serve as a better search model in molecular replacement. By contrast, each reference relied upon by the Examiner teaches the use of a structure of a single biomolecule.

In regard to Podjamy, et al., the reference acknowledges in the first line of the introduction (Section 1) that "the molecular replacement method has become a widespread and powerful technique for solving the phasing problem when a structure closely related to the one under study (or a fragment of it) is available." Podjamy, et al. does not teach what to do when a structure is not available or how to select a structure to use as the search model.

Podjamy, et al. states at the last line of Section 2 that "the purpose of this paper is to develop the necessary changes to make AmoRe work at very low resolution images." In Section 3, entitled, "LOW RESOLUTION MR. TESTS WITH AN ATOMIC MODEL", Podjamy, et al. teaches the use of a single search model of a single biomolecule at different resolution ranges. Specifically, Podjamy, et al. teaches at page 12, Section 3.2 that

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In order to find the right protocol for searches at low resolution, diffraction data calculated from **the atomic model** without solvent modelization were used at various resolution ranges.

Podjarny, et al. helps to expand how molecular replacement can be performed **once** an appropriate search model is identified. Podjarny, et al., however, does not teach or suggest methodology for selecting a particular search model from amongst a series of known search models to use in molecular replacement. This methodology uniquely resides in the present application.

Vitali, et al., like Podjarny, et al., teaches the use of a search model of a single biomolecule, namely the constant and variable domains of mouse Ig McPC603. Vitali, et al., does not, by contrast, teach how to select the particular Ig or other type of biomolecule to base the search model upon.

The Examiner is respectfully requested to withdraw the pending rejection for obviousness and allow all of the claims in view of the clear distinctions between Podjarny, et al., Vitali, et al., and the claims.

#### **Rejection Under 35 USC 102(b)**

The Examiner rejects claims 1-7, 16, 21-25, 31-36, 38, 40, 42, 45, 48 and 52-57 under 35 USC 102(b) on the grounds that the claims are anticipated by Podjarny, et al. and Vitali, et al.

The Examiner is respectfully requested to withdraw the pending rejection for anticipation and allow the claims in view of the clear distinctions between Podjarny, et al., Vitali, et al., and the claims and the remarks set forth above.

#### **Inappropriate Use of Official Notice**

Applicants wish to traverse the Examiner's implicit use of official notice in the Office Action. Specifically, at page 5 of the Office Action, the Examiner states

Therefore, it would be obvious to an artisan that in order to determine position and orientation of the target molecule by molecular

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replacement method, one must have a search model. To this end, it would be obvious to one skilled in the art at the time the invention was made to be motivated to perform multiple molecular replacement searches to identify a "search model" best suited for molecular-replacement determination of the structure of the target molecule. Obviously, in order to determine the best suited "search model" will require performing multiple replacement searches on more than one (i.e., multiple) potential "search models."

None of the references relied upon by the Examiner teach any methodology whatsoever for selecting the structure of one biomolecule relative to the structures of other biomolecules for use as the search model. In particular, the references do not teach or suggest how to compare search models to determine which search model will be the most effective.

By contrast, the present invention teaches how to conduct these comparisons and furthermore shows the unexpected effectiveness of differentiating different potential search models. The Examiner's attention is drawn, for example, to Figure 3 which illustrates that very few biomolecules (4 biomolecules) out of the pool tested (3245 biomolecules) were found to be good search models for the target molecule (xylose isomerase) using the method of the present invention. See Specification, page 40, line 29 - page 41, line 2 (""). As the Examiner can see, finding the proverbial needle in the haystack good structural model is in fact very hard and requiring of the creative and novel solution provided by the present invention. In the future, the Examiner is respectfully requested to find prior art that specifically teaches the limitations specified in Applicants' claims, including the dependent claims, which each specify different specific nuances regarding how to perform the methods of the present invention.

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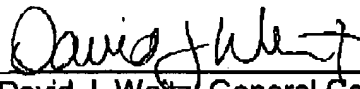
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**CONCLUSION**

Applicants earnestly believe that they are entitled to a letters patent, and respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

Respectfully submitted,  
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